B5 concld

is selected from the group ~~consisting of genes, oligonucleotides, antisense oligonucleotides, triplex DNA~~ compounds, and ribozymes.

B6 sub B2

16. (Amended) The method of Claim 9 further comprising an expression vector, wherein the compound [capable of altering nucleic acid sequence function] <u>for altering gene activity</u> is a nucleic acid sequence contained in the expression vector, and the expression vector is capable of expressing the nucleic acid sequence.

REMARKS

The above-identified patent application is a continuing-prosecution application Serial No. 09/457,771, filed December 9, 1999, which is now abandoned. Claims 1-16 are pending. Applicants have amended Claims 1, 5, 6, 8, 9 13, and 16. Support for these amendments can be found in the specification at page 1, line 33 – page 3, line 9. No new matter is contained in the amended claims. The following Remarks are provided in Response to the Final Office Action issued in application Serial No. 09/104,088, mailed September 10, 1999. Based on the foregoing amendments and the following Remarks, Applicants respectively request consideration and allowance of the pending claims.

CLAIMS OBJECTIONS

Claims 6 and 7 were rejected as dependent upon each other. Claim 6 has now been amended, to depend from Claim 1. Claim 7 is dependent upon amended Claim 6. Therefore, Applicants respectfully request that this rejection be withdrawn.

REJECTION UNDER 35 U.S.C § 112, FIRST PARAGRAPH

Claims 1-16 have been rejected under 35 U.S.C § 112, first paragraph, as containing subject matter not described in the specification in such a way as to enable one of ordinary skill in the art to make and/or use the invention. Applicants respectfully traverse this rejection.

The Examiner stated that the claims of the present application "are broadly directed to methods and compositions for delivering genes or gene products into the body for therapeutic purposes which are not enabled by the specification in view of the highly unpredictable and complex nature of the subject". The Examiner further stated that "[t]he claimed invention broadly encompasses the transfer of all types of nucleic acids (e.g. genes, oligonucleotides, RNA) into any and all cell types, tissues, and animals, including humans, such that one of skill in the art would be unable to practice the invention without undue experimentation, or with a reasonable chance of success."

The effectiveness of the block copolymers in delivering a compound for altering gene activity, as disclosed in the present application, is demonstrated by several Examples presented in the specification. Thus, a composition comprising block copolymer 1190 and plasmids bearing the gB or gD genes of the Herpes simplex virus delivered the gB or gD genes to mice. The genes were expressed as proteins, and antibodies directed to the virus were generated. (Example XIII at page 30).

Similarly, a cDNA encoding the hemagglutinin-esterase glycoprotein of bovine coronavirus was expressed in mice to give the encoded protein product after co-administration of the cDNA and the copolymer 1029.

Extensive details of the procedure used are presented in Example XII at pages 28-29 and Example VI, page 23.

Therefore, the specification shows that copolymers of the present invention are suitable carriers for therapeutic administration of genetic material to an animal. The above-mentioned Examples, presented in the specification, show that when widely differing genes are administered to animals by the methods and compositions of the present invention, the nucleic acids are biologically active. The administered genes are expressed, and the resulting proteins induce antibody formation. Optimization steps, such as determining the optimum nucleic acid or copolymer concentrations to use, would be routine to one of ordinary skill in the art.

Applicants have also demonstrated that compositions comprising copolymers and compounds for altering gene activity significantly increase transfection yields as compared to controls not containing the copolymer (Example IX, Table III). While there is variation in the effectiveness of the different copolymers, this is only in the degree of overall improvement of transfection. Surprisingly, the compositions of the present invention improved the viability of cells from 5-39%, as compared to a commercial transfection agent (Example XI at page 28; Table IV). Compositions of the present invention were able to transfect nucleic acid.

The Examiner specifically refers to the data of Example IX, wherein copolymer 1187 "at 5% transduction, performed the best of the five." Copolymer 1187, with a polyoxypropylene (POP) molecular weight of about 750 and a polyoxyethylene (POE) content of about 25% (Table II at page 17) is encompassed in Claim 1, that recites a copolymer "wherein the molecular weight represented by the polyoxypropylene portion of the copolymer is between approximately 750-15,000 and the molecular weight represented by the

polyoxyethylene portion of the copolymer constitutes less than 50% of the copolymer." Compositions comprising copolymers CRL-1183 and CRL-8131, also specifically pointed out by the Examiner, function as nucleic acid delivery vehicles. While these two compositions, with the particular nucleic acids and recipient cell lines used, had a similar percentage of transcription as did dextran/glycerol, this does not detract from their overall functionality. Furthermore, there is a marked improvement in the viability of the recipient cells with the copolymers of the present invention compared to a dextran/glycerol composition. Applicants, as presented in Example XIII, have also shown that enough cells can be delivered *in vivo* to protect transfected mice from a subsequent viral assault

Applicants, therefore, have demonstrated that copolymers with a POE content of 25% or less are effective transfecting agents and are capable of delivering a nucleic acid into cells in an animal. The transfection mediated by the copolymers of the present invention affords a therapeutic advantage to the recipient animal. Therefore, Applicants respectfully request withdrawal of this rejection.

REJECTION UNDER 35 U.S.C § 112 – SECOND PARAGRAPH.

Claims 5, 8 and 16 were rejected under 35 U.S.C § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that the inventor regards as the invention.

The Examiner stated "[t]he phrase "nucleic acid sequence" of Claims 5, 8, 16 is indefinite because it is unclear exactly what is to be delivered with the copolymer." Claims 5, 8 and 16 have been amended to replace the phrase "nucleic acid sequence" with "gene activity" as defined in the

specification at pages 1-2. Applicants, therefore, respectfully request that this rejection be withdrawn.

Claims 8 and 16 were rejected under 35 U.S.C § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that the inventor regards as the invention. The Examiner stated that "[t]he phrase "capable of expressing" in Claims 8 and 16 is open to interpretation and renders the claims indefinite as to their metes and bounds." Claims 8 and 16 have been amended to omit this phrase. Applicants therefore respectfully request that this rejection be withdrawn.

REJECTION UNDER 35 U.S.C § 103.

Claims 1-16 were rejected under 35 U.S.C § 103 (a) as unpatentable over *Simons et al., Hunter* (U.S. Patent No. 5,030,488), and *Allison et al.* (U.S. Patent No. 4,722,466).

The Examiner stated that "Allison and Hunter in combination disclose the POP molecular weight range and the percent POE range claimed by applicant. Both Hunter and Allison provide the motivation to use block copolymers with a POP molecular weight range of 950-15,000 and a POE percent of 1-90%." The Examiner summarized the teachings of the art by finding it would have been obvious "to deliver nucleic acids with a POP-POE copolymer as taught by Simons, and to use a POP-POE copolymer within the specific POP molecular weight of POE percent weight ranges described by Hunter and Allison to deliver a variety of pharmaceutical products with increased therapeutic efficacy." Applicants submit that the art cited does not render the presently claimed invention obvious.

Neither Simons nor Hunter teach the compositions or methods of the present invention, because both Simons and Hunter teach use of

copolymers having a 50-90% POE content. POP-POE copolymers having differing POE percentages are chemically different compounds and do not provide teachings for other uses of POP-POE copolymers. The copolymer used in Simon forms a hydrogel due to its high POE content.

Allison does not provide the missing element for an obviousness teaching because Allison does not teach the range of copolymers found in the currently claimed invention. Allison teaches an adjuvant that uses smaller molecular weight POP copolymers in emulsions with a required glycoprotein to stimulate a classical immune response. The copolymers of Allison have total molecular weights of 1,000 to 16,000. (page 3, lines 52-59). The preferred copolymers of Allison have a POP of 2250 to 4300 and POE of 1% to 30%. See Col. 4, lines 17-20. Additionally, Allison does not render Applicants' claimed invention obvious because Allison teaches a composition with the required combination of a copolymer with a surfactant and an immunopotentiating glycopeptide. In fact, Allison teaches away from using copolymers in compositions without the required addition of a glycopeptide; "it is clear that to elicit a powerful cell-mediated and humoral response, the combination of glycopeptide and PLURONIC® polyol is essential." See Allison, Col. 13, lines 50-53. Allison teaches that classical immunization can be achieved but only in the presence of a glycopeptide and Hunter and Simon teach a chemical composition that is not found in Applicants' presently claimed invention. The combination of these three does not teach use the compositions of the present invention in the methods of the present invention. Thus, Applicants submit the cited art does not render the presently claimed invention obvious.

The foregoing is submitted as a full and complete Response to the Office Action mailed September 10, 1999, in the related application. This Amendment places all considered claims in the present application in condition for allowance, and such action is courteously solicited. The

Examiner is invited and encouraged to contact the undersigned attorney of record if such contact would facilitate an efficient examination and allowance of the application. The Commissioner is hereby authorized to charge any additional fees required under 37 C.F.R. § 1.16, or credit any overpayment, to Account No. 10-1215.

Respectfully submitted,
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